## Remarks

In the November 17, 2004 Office action, claims 1-46 were pending. After the present amendment, claims 1-29, 31, 35-38, 40-45, and 47-74 are pending. Reconsideration of the rejection is requested.

## Section 112 Rejections

Claims 1-46 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claim 1 was said to be indefinite because it was unclear where the mobilization zone is located in the path of liquid flow. Claim 1 has been amended to clarify that the path of liquid flow is from the sample application area, distally through the mobilization zone to the primary capture area and then to the secondary capture area. Support for this amendment is found in the specific embodiments shown in FIGS. 1 and 2, as well as the description of those embodiments in the specification at page 7, lines 1-12; page 16, lines 14-20; and page 18, lines 10-26.

Claims 2, 6, 8, 9, 11, 12, 15-19, 16, 20, 21, 23 and 29 have similarly been amended to overcome the rejections. For example, claims 11 and 15-19 were amended to overcome the lack of antecedent basis, and to spell out the well-known terms for which the acronyms HIV and HTLV were previously given.

Claim 31 was amended to correlate the body of the claim with the preamble.

Claims 33-34 were said to be indefinite because they specified how the tracer was applied to the test strip. Applicant disagrees that this product-by-process claim is indefinite, but the claims have been amended to advance prosecution. The relative term "sufficient" in claim 42 has been deleted from the claim to overcome the rejection.

## Support for New Claims

The new claims are similar to many of the prior claims, and are supported throughout the specification.

For example, claim 49 calls for the detectable tracer to "interact with the test strip." The specification provides numerous examples of how the tracer "interacts with the test strip" to slow movement of the tracer along the path of liquid flow. Page 20, lines 26-31, states that the interaction can be achieved with a very large conjugate molecule (such as bovine serum albumin) that moves slowly through the test strip. Other examples that are given at page 21, lines 1-5,

include the size, polarity or charge of the A-L-T conjugate. Page 21, lines 6-10, provides examples of specific sizes of colloidal gold particles that can be selected "depending on the migration characteristics desired." Page 24, lines 26-31, describes delayed-release reversible immobilization using co-molecules such as sucrose, mannitol, glycerol, PVA or PVP. The embodiment of FIG. 2 described on pages 17-18 is entitled "A-L-T Conjugate Mobilization Zone Under Sample Pad," and it describes a test strip in which the conjugate tracer is present deep in the test strip, such that the superficially applied sample encounters less resistance than the conjugate tracer. This difference allows the sample to interact with the test strip in a way that it migrates through the pad more quickly than the subjacent conjugate migrates (page 18, lines 16-20).

Given these many different examples of interaction of the tracer with the test strip, one skilled in the art would understand the meaning of claim 51. The disclosure of these many different species within the genus of "interaction" with the test strip demonstrates that the generic term used in claim 51 is both clear and appropriate.

New claims 50-74 are similar to claims that were previously presented, and are supported by the original disclosure.

New claim 63 is supported by the Summary at pages 5-7 of the original specification.

Claim 64 is supported at pages page 5, line 30 to page 6, line 2 and at page 12, lines 16-20; claim 66 at page 5, lines 26-29; claim 67 at pages 17-18, especially at page 18, lines 16-20; claim 68 at page 18, lines 16-20; claim 69 at page 20, line 26 to page 21, line 3; claim 70 at page 20, line 26 to page 21, line 3; claim 71 at page 5, lines 26-29; claim 72 at page 21, lines 3-5; claim 73 at page 21, lines 6-13; and claim 74 at page 20, line 26 to page 21, line 3.

## Section 102 Rejections

The claims have been amended to overcome the anticipation rejections that were made under 35 USC Section 102.

For example, with respect to claim 1, none of the cited references disclose a path of liquid flow from the sample application area distally through the mobilization zone to the primary capture area and then to the secondary capture area, wherein (a) the detectable tracer is present on the test strip in a position that a distal flow of analyte reaches the primary capture area before a distal flow of tracer reaches the primary capture area (b) such that subsequent binding of

detectable tracer to first immobilized binding partner is inhibited and unbound detectable tracer continues along the path of flow distally to the second immobilized binding partner (c) to provide a signal from the secondary capture area that indicates the presence of the analyte in the liquid sample.

As noted in the Office action, Friesen et al. fails to teach a secondary capture area with an immobilized binding partner having a binding affinity for the analyte and a binding affinity for the detectable tracer.

The Office action also notes that Boehringer et al. does not disclose a specific device in which the detectable tracer is said to migrate through the device at a rate slower than a rate at which the analyte in the sample migrates through the device.

Luo et al. similarly fails to disclose modifying the migration rate of the tracer as claimed.

**Section 103 Rejections**

The pending claims were rejected in view of Friesen et al. (U. S. Patent No. 5,229,073) in combination with a variety of secondary references. For example, claims 1, 2, 7-8, 10-15, 20-25, 28-32, 35-36, and 39 were rejected as unpatentable over Friesen et al. in view of Luo et al. (U.S. Patent No. 5,229,073). The Office action alleged that Friesen et al. disclosed a test strip in FIG. 2 wherein the sample application zone was located downstream of the mobilization zone I and the reagent zone II. It was said that when sample was applied to the strip, it could flow toward the reagent zone II and toward the mobilization zone I, such that sample would reach the reagent zone II before tracer in mobilization zone I reached the reagent zone. The Office action noted at page 7 that such an interpretation was possible because it was unclear where the mobilization zone was located on the strip.

Claim 1 now clarifies that the path of liquid flow moves from the sample application area distally through the mobilization zone to the primary capture area. The cited references do not disclose a test strip having this unidirectional configuration, in which the analyte reaches the primary capture area before the tracer reaches the primary capture area. Hence the cited references do not establish a prima facie case of obviousness with respect to claim 1, or any of the claims that depend from claim 1. Moreover, the claimed configuration of claim 1 provides a test strip in which the analyte can occupy the binding partner of the primary capture zone, such

that subsequently arriving tracer can move unidirectionally through the primary capture zone to the secondary capture zone.

Original claim 3 was directed to a device in which the detectable tracer migrates through the test strip at a rate slower than the analyte, and original claim 4 specified that the slower migration was caused by the molecular weight of the tracer. Claims 3 and 4 were rejected under 35 USC Section 103(a) as obvious in view of Boehringer et al. This reference was said to differ from these claims because Boehringer et al. did not disclose the slower rate of migration. However, that reference was said to disclose at pages 43-45 an analyte analog on BSA coated latex microspheres having a diamter of 0.51 microns. The Office action asserted that it would have been obvious that a slower rate of migration could be achieved with the disclosed coated latex microspheres.

Amended claim 1 now states that the detectable tracer is positioned in the path of flow on the test strip in a position that a distal flow of analyte through a bibulous substrate reaches the primary capture area before a distal flow of the tracer. See, for example, the specification at page 24, lines 17-31 (components are arranged on substrate so analyte contacts primary capture zone first), and the embodiment of Fig. 2 described at page 18, lines 16-20 (deeper placement of conjugate and placement under pad slow migration of analyte). Boehringer et al. neither discloses nor suggests such an arrangement. Although the reference does disclose a lateral flow device in which liquid flows from a sample pad to a labeling zone to a barrier and capture zone, it fails to establish a prima facie case of obviousness because it does not disclose or suggest the claimed limitations. For example, it is not clear from the Boehringer et al. reference whether a distance between the labeling zone and barrier zone is great enough to allow separation of the wave fronts of the label and analyte before they reach the barrier zone. As explained in applicants' specification at page 21, it must be determined in each instance whether the combination of tracer complexes, porous substrate, binding partners and other factors permit the separation of the analyte and tracer wave fronts. Since Boehringer et al. did not even appreciate the desirability of achieving this separation, they can not be said to have disclosed or suggested the claimed solution. Moreover, it can not be said that their selection of conditions (such as substrate pore size and chemical and physical characteristics of the tracer and analyte, and the distance between the sample application zone and the barrier zone) produced the claimed result.

The Boehringer reference can not be said to disclose migration of an analyte in advance of a labeled conjugate. As shown in the attached Declaration of Robert Buck, a large conjugate and analyte can flow together into the primary capture zone if the distance of travel between the position of the conjugate and the primary capture zone is not sufficient to permit the separation of the conjugate and analyte. Boehringer does not disclose or suggest differential migration of the analyte and conjugate, nor does it demonstrate any appreciation of the technical issues to be addressed to achieve this goal. It does not establish a prima facie case of obviousness with respect to the claimed test strip.

Moreover, the claimed placement of the detectable tracer on the test strip in a position that a distal flow of analyte reaches the primary capture area before a distal flow of tracer provides an expectedly superior result. As demonstrated in the attached Declaration of Robert Buck, such placement of the tracer provides greater sensitivity of test results by permitting more effective separation of the wave fronts. The Declaration discloses experiments in which, as a distance between the tracer and analyte was increased, a weaker signal was obtained from the primary capture area, indicating that more tracer was available for binding at the secondary capture area to provide a stronger signal that would indicate a positive result. Since Boehringer et al. does not even demonstrate an appreciation of the problem to be solved (effective separation of the analyte and tracer wave fronts to provide a better signal in the secondary capture zone), that reference can not be said to suggest the solution that has provided surprisingly superior test sensitivity.

The remaining Section 103 rejections are made in view of Friesen et al. as the primary reference. It is submitted that the amendments to claim 1, in which the path of flow is described from the sample application zone through the secondary capture zone, distinguishes these combinations of references.

**Other claims**

Claim 2 calls for the tracer to be positioned *within* the test strip in a position that the distal flow of tracer reaches the primary capture area after the distal flow of analyte. This claim is supported, for example, by FIG. 2 and the accompanying text at pages 17-19, wherein the tracer 154 is immobilized beneath an overlapping collection member 132 to slow the migration rate of the tracer. See the specification particularly at page 18, lines 16-20. The cited references

neither disclose nor suggest this claimed combination. Since the prior art does not even evince an appreciation for the problem being solved, it could not be said to suggestion this solution.

Claim 3 adds the limitation that the tracer is heavier than the analyte to the limitation of claim 1 that detectable tracer is present on the test strip at a position that the distal flow of analyte reaches the primary capture area before the tracer. The prior art does not disclose or suggest this combination. As already noted, Boehringer et al. does not take the placement of the tracer into account, and the illustrated embodiments show the labeling zone 14 to be quite close to barrier zone 16. Moreover, the labeling zone in that reference is depicted as a pad on top of the test strip, and is not within the test strip.

Claim 4 adds that the tracer is selected to interact with the test strip to slow migration of the tracer relative to migration of the analyte. None of the references show a tracer that is selected for this purpose. Since none of the references even appreciate the problem that is being solved, they can not be said to suggest this claimed solution. Moreover, the claimed solution provides superior sensitivity of the test strip, as noted in the attached Declaration.

Claims 5-9 are directed to particular examples of ways to slow migration of the tracer. Since the prior art does not suggest slowing the migration of the tracer, neither could it be said to suggest these particular approaches. Claim 5 is supported in the specification at page 20, line 26 through page 21, line 22; claim 6 is supported at page 24, lines 11-12; claim 7 is supported at page 21, lines 3-5; and claims 8-9 are supported at page 24, lines 22-31.

Amended claim 10 is supported at page 12, lines 16-20 and page 15, lines 3-8.

Claim 12 calls for the first binding partner to be an antibody having a greater affinity for the analyte than the analyte analog, as supported for example at page 16 lines 23-28 and page 19, lines 4-9. The combination of this affinity difference with the differential migration rates of claim 1 is not suggested by the prior art. The combination of these approaches provides a highly sensitive lateral flow assay.

Claim 14 calls for the detectable tracer to comprise a visually detectable label covalently attached to analyte or analyte analog (as supported in the specification, for example, at page 13, lines 13-14). This differs from Boehringer et al. in which the latex microspheres are coated with a PDG-BSA conjugate (see for example page 43 of that reference). The Boehringer et al. reference does not disclose or suggest covalently attaching the tracer to an analyte or analyte analog, and it therefore fails to establish a prima facie case of obviousness with respect to claim

14. Moreover, as explained in the attached Declaration, covalently binding the tracer to the analyte or analyte analog provides an improved assay system that reduces leaching of tracer from the analyte or analyte analog. Freer leaching from the passively "coated" microspheres of Boehringer et al. creates problems with the claimed assay because the leached analyte or analog functions as a "free analyte" that gives falsely elevated values in a positive reporting system. In the case of negative samples, this leads to a false positive reading. The attached Declaration states that conjugates made though passive absorption did not perform as well as the covalently attached conjugate because they showed leak-through for the negative control. The cited references do not even demonstrate an appreciation of this problem, much less can they be said to suggest the claimed solution.

Claim 22 is an independent claim to a bibulous test strip in which the detectable tracer comprises an analyte or analyte analog covalently coupled to the detectable label and the detectable label has been selected to have a slower rate of migration of the tracer than the analyte through the bibulous test strip. As noted in connection with claim 14, the cited references do not disclose the use of a label covalently bound to an analyte or analyte analog in the claimed assay to avoid the problem of leak through and false positives in the context of the claimed assay.

Claim 23 adds that the tracer comprises the analyte or analyte analog covalently linked to the detectable label by a linker molecule. This claim is allowable for the reasons set forth in connection with claim 22. Moreover, the covalent linker increases the effective size of the complex to help retard migration of the tracer complex through the bibulous substrate, without exceeding the pore size of the substrate, as described at page 21 of applicants' specification.

Claim 24 depends from claim 22 and adds the limitation (supported at page 21 of applicants' specification) that the detectable tracer is selected to be small enough to migrate through the bibulous test strip but not so large that it is trapped by pores of the bibulous test strip. The latex microspheres disclosed in Boehringer et al. are not selected in this manner. Boehringer et al. discloses (at page 47) microspheres that are 47 microns in size, which are somewhat larger than the latex particles disclosed in applicants' specification at page 21, lines 10-13. Boehringer et al. is silent about selecting tracers with respect to the pore size of a bibulous substrate, and it is believed that the Boehringer et al. microspheres could become trapped in pores and provide steric hindrance that would reduce the interaction between analyte or analog and its binding partner.

Claim 25 specifically claims latex particles falling within the range of sizes that works particularly well in a porous substrate such as nitrocellulose. These ranges are supported at page 21, lines 10-13 of applicants' specification, and are not disclosed in Boehringer et al.

Claim 26 calls for the detectable label to comprise a colloidal gold particle. The colloidal gold particle is particularly effective in the claimed assay because its small size permits it to flow through the pores of the bibulous substrate, while its heavier weight provides particularly effective retardation of migration of the tracer complex relative to analyte.

Claim 27 states that a linker molecule forms a stable covalent linkage between the detectable label and the analyte or analyte analog, as supported in the specification at page 14, lines 6-8. Claim 28 adds that the linker molecule comprises from 1-20 carbons and 0-10 heteroatoms, as supported at page 14, lines 12-13. This feature is not believed to be disclosed or suggested in the assays of the cited references, and do not establish a prima facie case of obviousness with respect to these claims.

Claims 31, 35-38, 40-45, and 47-49 depend from allowable claims or contain features that are independently patentable. Claim 45, for example, concerns a test kit containing instructions for use of the test strip such that flow of analyte in the liquid sample reaches the primary capture zone before the flow of tracer. Since the prior art does not disclose or suggest this feature, a prima facie case of obviousness has not been established with respect to this claim.

Claim 50 is a new claim to a method of making a test strip by providing a bibulous substrate that defines the path of liquid flow. In the mobilization zone is provided a detectable tracer coupled to analyte or an analyte analog, wherein the complex has been selected to migrate more slowly through the bibulous test strip than the analyte. The cited references do not disclose or suggest selecting such a complex that has been selected for this purpose. The Office action has contended that the test strip of Boehringer et al. could possibly disclose such a complex. Although applicants disagree that such a complex is disclosed in Boehringer et al., since the Office action agrees that the reference neither discloses nor suggests selecting a complex in this manner, the reference can not be said to establish a prima facie case of obviousness with respect to claim 50. Even if such a prima facie case of obviousness were found, however, any such assertion of obviousness would be rebutted by the evidence of superior assay sensitivity provided in the attached Declaration.

Claim 63 is another independent claim which calls for a detectable conjugate to flow more slowly through the porous test strip than the analyte flows through the test strip after liquid to be analyzed is applied to the proximal sample application area, such that binding sites in the primary capture area are already at least partially occupied by analyte when the detectable conjugate flow reaches the primary capture area. Although the Office action has alleged that Boehringer et al. discloses such a test strip, it is submitted that such an assertion is speculation that is unsupported by the reference. As noted in applicants' specification, many factors can affect whether there is a separation of the analyte and tracer wave fronts by the time the analyte reaches the primary capture area. The size of the particle and the pores of the substrate can have an effect on the separation characteristics. Moreover, the distance between the labeling zone and barrier zone in Boehringer et al. is depicted in FIGS. 1-3 as being quite close to one another. It is unclear that this very close proximity of the detectable conjugate to the primary capture area would be sufficient to permit the detectable conjugate and analyte to separate. Hence the assertion in the Office action that the claimed separation occurs, and that the analyte reaches the primary capture area before the detectable conjugate, is mere speculation based on hindsight reconstruction of the claimed invention in view of applicants' disclosure. Such hindsight reconstruction does not establish a prima facie case of obviousness, and claim 63 is therefore allowable.

Claims 64-74 add features that are also patentable in combination with claim 63.

## Obviousness Type Double Patenting Rejection

Claims 1-38 were rejected as being unpatentable over claims 1-15, 18-20 and 25-37 of U.S. Patent No. 6,699,722.

Applicants plan to submit a Terminal Disclaimer to overcome this rejection, but the necessary signatures have not yet been obtained on the Terminal Disclaimer. The executed Terminal Disclaimer will be filed as soon as it is available.

## Conclusion

Applicants have addressed the rejections raised by the examiner in the November 17, 2004 Office action. All the claims are believed to be in condition for allowance. If any matters

remain before a Notice of Allowance is issued, the Examiner is invited to telephone the undersigned attorney at the telephone number listed below.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By 

William D. Noonan M.D.
Registration No. 30,878

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 228-9446